IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Daniel F. Hanley et al.

Application No.: 10/509,694	Confirmation No.: 2172
Filed: September 29, 2004	Art Unit: 1614
For: INTRAVENTRICULAR HEMORRHAGE THROMBOSIS	Examiner: W. Webb

DECLARATION UNDER 37 C.F.R. 1.132

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Daniel F. Hanley, a citizen of the United States of America residing at 1204 Berwick Road, Towson, Maryland 21204 hereby declare as follows:

1. I am an inventor of the subject matter described and claimed in the patent application U.S.S.N. 10/509,694, filing date September 26, 2005 which is a Continuation Application of PCT/US03/09939, filing date March 29, 2003, and otherwise identified above.

2. I have read and understood the Office Action dated March 3, 2009, and the reference cited therein.

3. The following experiments were conducted by us or under our supervision, subsequent to the filing date of the above-identified application but according to the methods disclosed in the application.

(I) Experiment I:

Study subjects (n=42) were patients with a spontaneous intracerebral hemorrhage (ICH) and an associated intraventricular hemorrhage large enough to require external ventricular drainage (EVD) for the treatment of obstructive hydrocephalus. The decision to treat with EVD was distinct from the study protocol and was made by a treating physician prior to enrollment into the study. Therefore, no patient was exposed to the risk of EVD who otherwise would not have received EVD for conventional treatment. Patients or their family members were approached for informed consent only after EVD had been instituted.

In a double-blind study, patients were randomized into three groups and tissue plasminogen activator (t-PA) was delivered directly onto the clot by catheter using one of three dosing regimens: 3.0 mg every 12 hours (3.0mg q12h) (n = 26), 1.0 mg every 12 hours (1.0mg q12h) (n = 8), or 0.3 mg every 12 hours (0.3mg q12h) (n = 8). Patients were dosed up to 8 times until the IIIrd and IVth ventricle were open. Patient progress was tracked using routine methods.

(II) Experimental Results:

Direct comparison of the initial clot lysis rate (first three days of treatment) estimated dose specific rates of 23%, 27.5%, and 22% (of stability CT scan volume)/day for the 3 mg, 1.0 mg, and 0.3 mg groups. The safety profile for the two lower doses was numerically superior to the 3.0 mg dose. Specifically, no symptomatic bleeding occurred at either of the lower dose levels, 0.3 mg and 1.0 mg/dose. A blinded central analysis of C/D data did not demonstrate a significant difference in catheter tract bleeds. A trend towards minor bleeds (> 5 mm, confluent) to occur with 1.0 vs. 0.3 mg drug exposure can be observed. There were no episodes of bacterial ventriculitis for either dose. One death (13%) occurred in each group.

From a direct comparison of the efficacy and side effect profile of the three doses the 0.3 mg dose appeared to offer the highest rate of clot lysis with the lowest complication rate. However, based on the clot lysis rate, the 1.0 mg dose offers the best demonstrated clot lysis rate with an acceptable safety event rate.

(III) Experiment II:

Study subjects (n = 36) were patients with a spontaneous intracerebral hemorrhage (ICH) and an associated intraventricular hemorrhage large enough to require external ventricular drainage (EVD) for the treatment of obstructive hydrocephalus. The decision to treat with EVD was distinct from the study protocol and was made by a treating physician prior to enrollment into the study. Therefore, no patient was exposed to the risk of EVD who otherwise would not have received EVD for conventional treatment. Patients or their family members were approached for informed consent only after EVD had been instituted.

Patients were placed in a single group and tissue plasminogen activator (t-PA) was delivered directly onto the clot by catheter using one dosing regimen of 1 mg every 8 hours. Patient progress was tracked using routine methods.

(IV) Experimental Results:

(A) Clinical outcomes

Primary endpoint determined at 30 days for a subset of subjects (n = 36) were death (19%), symptomatic bleeding (8%), and bacterial ventriculitis (3%). It is noted that all of the deaths were a result of the initial severity of the initial bleeding event and withdrawal of care. None of the deaths were attributed to bleeding or ventriculitis. Further it is important to note that the event rates observed are exceedingly low as compared to historical rates.

(B) Functional outcomes

Functional outcome results for the 1mg q8h group demonstrate 43% of subjects (n = 36) were modified Rankin Score (mRS) 0-4 at thirty days and this group's functional state improved over the next 5 months so that 49% of subjects were mRS 0-3 at 180 days (see figure below). This 180 day group included 6%, 11%, 14% and 17% as mRS 0, 1, 2, and 3 respectively. The median NIH stroke scale of this entire mRS 0-3 group was 1 (ave 1.6) and the median Barthel score was 100 (ave 94). The average 180 day stroke impact scale (SIS)-16 score was 4.5 / 5. Thus the functional profile of this group of mRS 0-3 individuals supports their ability to be independent in the home at 180 days.

(IV) Combined results for Experiments I and II

Combined Experiments I and II included 78 treatment subjects and 22 placebo subjects. The data safety monitoring board (DSMB) thresholds for the studies were the same, mortality 55%, rebleeding 35%, and ventriculitis 30%. No safety threshold was crossed in the experiments. The observed 30 day outcome rates for the combined 0.3 mg q12h, 1.0mg q12h, and 1.0mg q8h groups were mortality 17%, symptomatic rebleeding 6%, and bacterial ventriculitis 2%. The observed rates of events for each of the treatment groups is shown in the table below:

Dose	# Subjects	Dead	Bleeding, Symptomatic	Ventriculitis, Bacterial
Placebo	22	23%	5%	9%
3.0 mg, q 12	26	19%	23%	8%
1.0 mg, q 12	8	13%	0%	0%
0.3 mg, q 12	8	13%	0%	0%
1.0 mg, q 8	36	19%	8%	3%

These data demonstrate the safety of the low dose administration protocols of tPA, with decreased symptomatic bleeding as compared to higher doses of tPA, and safety was comparable to patients receiving placebo.

(V) Conclusions

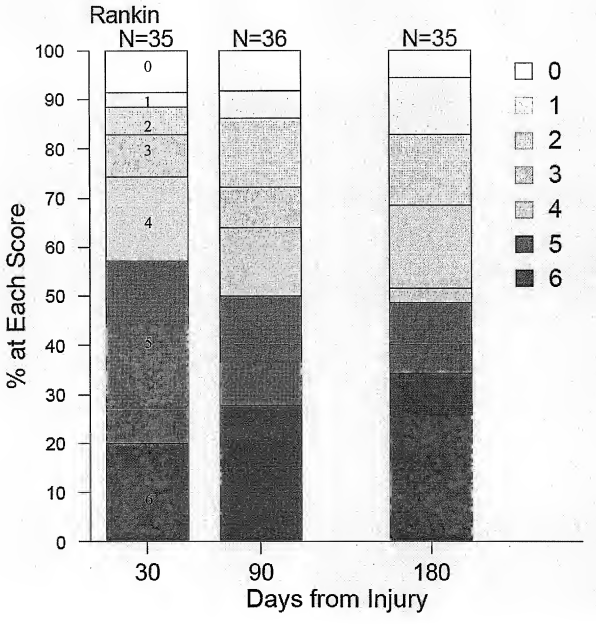
Administration of low serial doses of tPA (1 mg or 0.3 mg per dose) is useful for the treatment of spontaneous intracerebral hemorrhage and an associated intraventricular hemorrhage and reducing clot size, providing a better safety profile and at least as good an efficacy profile as higher dose tPA. The low actual mortality (less than 20%) compared to expected mortality in the 60 to 80% range strongly suggests that removal of blood from the ventricles is beneficial to individuals with IVH. The functional independence of the majority of these individuals suggests the outcomes of treatment can be favorable. The 49% rate of favorable outcome is unique and markedly improved compared to the literature rate of 10% (ref Nieukamp DJ et al; Journal of Neurology 2000 Feb;247(2):117-21.).

4. I, the undersigned Daniel F. Hanley further declare that all statements made herein of my own knowledge are true and that all statements made upon information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 101 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the above identified application or any patent issuing thereon.

Daniel F Hanley

By:_____
Daniel F. Hanley

Date: September 30, 2009



Functional outcomes for subjects administered tPA 1mg q8h. See section IV(B).